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Structural and functional characterization of microcin C resistance peptidase MccF from *Bacillus anthracis*

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Microcin C (McC) is heptapeptide-adenylate antibiotic produced by *Escherichia coli* strains carrying the *mccABCDEF* gene cluster encoding, in addition to the heptapeptide structural gene *mccA*, enzymes necessary for McC biosynthesis and self-immunity of the producing cell. The heptapeptide facilitates McC transport into susceptible cells, where it is processed releasing a non-hydrolyzable aminoacyl adenylate that inhibits an essential aspartyl-tRNA synthetase. The self-immunity gene *mccF* encodes a specialized serine-peptidase that cleaves an amide bond connecting the peptidyl or aminoacyl moieties of, respectively, intact and processed McC with the nucleotidyl moiety. Unlike in *E. coli*, some of *mccF* orthologs are not expressed as a part of the *mcc* operon, and exist as single genes. Here, we show that a protein product of one such gene, MccF from *Bacillus anthracis* (*Ba*MccF), is able to cleave intact and processed McC. Structural analysis conformed this observation. The structures of apo-*Ba*MccF and its AMP-complex revealed a peptidase with specific features that allow MccF to interact with substrates containing nucleotidyl moieties. Sequence analysis and phylogenetic tree reconstruction for the MccF/LD-carboxypeptidase family of proteins show distinct subfamilies in the MccF clade. Several representatives of MccF clade can restore *E. coli* resistance to McC and other non-hydrolyzable aminoacyl adenylates. Based on our data we propose that members of MccF clade may have similar substrate specificity. Our results suggest that expression of widespread *mccF*-like genes may be linked to detoxification of aminoacyl adenylates (endogenous or exogenous) and may represent a "stealthy" source of antibiotic resistance.